

Commentary

Sulfatide Inhibits Growth of Fibroblasts and Is a Potential Treatment against Fibrosis

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ABSTRACT: Fibrosis of vital organs such as the lungs, liver, and kidneys is a serious condition without effective causal treatment. Here, we suggest the use of the sphingolipid sulfatide and its isoform C16, which we have found to inhibit the growth of fibroblasts. In the lungs, sulfatide can be easily administered via an inhalation spray. Alternatively, fenofibrate, an anti-cholesterol drug with no major side effects, may be used, as it enhances the body's own production of sulfatide.

Keywords: Sulfatide; Fibroblast; Fibrosis; Lung; Liver; Kidney; MASH; NAFLD



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For several important organs, fibrosis-related diseases are classical disorders. Examples include lung fibrosis, liver fibrosis, and kidney fibrosis. Lung fibrosis is observed in restrictive lung insufficiency, in which the membrane between the alveoli and lung capillaries becomes thickened [1]. As a result, the diffusion of oxygen from air to blood, and of CO₂ in the opposite direction, is restricted, leading to dyspnea. This disease is severe, with limited treatment options and a poor prognosis of only 3–5 years after diagnosis [1]. Lung transplantation may be urgently required, but it is, of course, out of practice for many patients.

Hepatic fibrosis is often seen in the early development of cirrhosis. It may be caused by high alcohol intake [2] or by obesity due to dysregulation of glucagon, glycogen, and gluconeogenesis [3]. Although relatively common and initially without dramatic symptoms, its progression is serious and potentially fatal. Fibrosis consists of connective tissue infiltrating the liver cell architecture, which disrupts normal liver function. This can cause portal hypertension, ascites, and esophageal bleeding [4]. Furthermore, metabolic dysfunction associated steatohepatitis (MASH), with additional hepatic fibrosis, is today the primary reason for liver transplantation [5].

Kidney fibrosis is frequently observed following diseases that alter renal structure and function, such as diabetes, hypertension, and nephritis [6]. The accumulation of connective tissue in the kidneys impairs urine concentration capacity, which may ultimately cause uremia.

There are no effective causal treatments for all three conditions, and in advanced stages, the prognosis is poor. We recently published that sphingolipid sulfatide, especially its isoform C16 sulfatide, can inhibit fibroblasts and thereby prevent connective tissue formation [7]. The idea for this study arose from the observation that insulin injections often induce local fibrosis in subcutaneous tissue, requiring daily changes of injection sites in insulin-treated diabetic patients. Interestingly, such fibrosis is not seen in the pancreas, where sulfatide is present together with insulin. In our study, sulfatide and C16 sulfatide were shown to inhibit fibroblast growth at concentrations of 30 µM [7].

The first step of sphingolipid biosynthesis, and thus of sulfatide, is the condensation of serine and palmitoyl-CoA, catalyzed by serine palmitoyl transferase (SPT). Several molecules inhibit SPT, some isolated from fungi. For example, myriocin, derived from *Isaria sinclairii*, and sphingofungin B, derived from *Aspergillus fumigatus* [8], both inhibit SPT and thereby sulfatide biosynthesis. After harvesting, wheat must be stored properly to prevent fungal growth under humid conditions. *Aspergillus fumigatus* is often found in poorly stored wheat grain [9]. Thus, the presence of *A. fumigatus* and sphingofungin B in wheat could impair sulfatide biosynthesis in humans and should be avoided.

We hereby propose the use of sulfatide or C16 sulfatide for causal prevention or early treatment of fibrosis in the various organs. For lung fibrosis, inhalation delivery seems straightforward. For hepatic and kidney fibrosis, treatment is more challenging. Sulfatide is relatively expensive to produce or isolate, but the cholesterol-lowering drug fenofibrate may be used instead; this drug has been shown to increase sulfatide levels in mice, is nontoxic, and has been used safely for many years [10]. However, it must be stressed that no clinical studies of sulfatide in fibrosis have yet been performed, and the treatment may not be effective in all types of fibrosis.

In conclusion, we propose the use of sulfatide against fibrosis. Administration in the lungs is relatively simple, whereas strategies that enhance endogenous sulfatide production, such as fenofibrate treatment, may be more feasible for the liver and kidneys.

Author Contributions

Conceptualization, K.B.; Writing—Original Draft Preparation, R.T. and K.B.; Writing—Review & Editing, R.T. and K.B.

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Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Koudstaal T, Funke-Chambour M, Kreuter M, Molyneaux PL, Wijsenbeek MS. Pulmonary fibrosis: From pathogenesis to clinical decision-making. *Trends Mol. Med.* **2023**, *29*, 1076–1087. doi:10.1016/J.MOLMED.2023.08.010.
2. Caputo F, Penitenti F, Bergonzoni B, Lungaro L, Costanzini A, Caio G, et al. Alcohol use disorders and liver fibrosis: An update. *Minerva Med.* **2024**, *115*, 354–363. doi:10.23736/S0026-4806.24.09203-6.
3. Galsgaard KD. The Vicious Circle of Hepatic Glucagon Resistance in Non-Alcoholic Fatty Liver Disease. *J. Clin. Med.* **2020**, *9*, 4049. doi:10.3390/JCM9124049.
4. Bataller R, Brenner DA. Liver fibrosis. *J. Clin. Investig.* **2005**, *115*, 209–218. doi:10.1172/JCI24282.
5. Younossi ZM, Stepanova M, Al Shabeeb R, Eberly KE, Shah D, Nguyen V, et al. The changing epidemiology of adult liver transplantation in the United States in 2013–2022: The dominance of metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease. *Hepatol. Commun.* **2024**, *8*, e0352. doi:10.1097/H9.0000000000000352.
6. Yamashita N, Kramann R. Mechanisms of kidney fibrosis and routes towards therapy. *Trends Endocrinol. Metab.* **2024**, *35*, 31–48. doi:10.1016/J.TEM.2023.09.001.
7. Roeske-Nielsen A, Månsson JE, Tekin H, Rieneck K, Bendtzen K, Buschard K. Sulfatide inhibits fibroblast growth, activation and oxidative stress induced by ectopic insulin. *Diabetes Obes. Metab.* **2023**, *25*, 2514–2525. doi:10.1111/DOM.15123.
8. Delgado A, Casas J, Llebaria A, Abad JL, Fabrias G. Inhibitors of sphingolipid metabolism enzymes. *Biochim. Biophys. Acta* **2006**, *1758*, 1957–1977. doi:10.1016/J.BBAMEM.2006.08.017.
9. Sadhasivam S, Britzi M, Zakin V, Kostyukovsky M, Trostanetsky A, Quinn E, et al. Rapid Detection and Identification of Mycotoxigenic Fungi and Mycotoxins in Stored Wheat Grain. *Toxins* **2017**, *9*, 302. doi:10.3390/toxins9100302.
10. Holm LJ, Haupt-Jorgensen M, Giacobini JD, Hasselby JP, Bilgin M, Buschard K. Fenofibrate increases very-long-chain sphingolipids and improves blood glucose homeostasis in NOD mice. *Diabetologia* **2019**, *62*, 2262–2272. doi:10.1007/S00125-019-04973-Z.